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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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David G. Gorenstein

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EXAMINER

STEELE, AMBER D

ART UNIT

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/828,934	Applicant(s) GORENSTEIN ET AL.	
	Examiner Amber D. Steele	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-78 is/are pending in the application.
- 4a) Of the above claim(s) 12-77 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 78 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/18/07; 8/27/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 22, 2008 has been entered.

Status of the Claims

2. The amendment to the claims received on October 4, 2006 amended claim 7.

The amendment to the claims received on June 25, 2007 amended claim 7 and added new claim 78.

The amendment to the claims received on February 22, 2008 amended claim 1.

Claims 1-78 are currently pending.

Claims 1-11 and 78 are currently under consideration.

Election/Restrictions

3. Applicant's elected Group I (claims 1-11 and new claim 78) without traverse in the reply filed on October 4, 2006. Claims 12-77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Priority

4. The filing date (April 21, 2004) of the present application is the priority date for the presently claimed invention.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on August 27, 2007 and September 18, 2007 are being considered by the examiner.

Please note: The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a). The references in the search report have only been considered if listed separately on the IDS and a copy of the reference was supplied where applicable.

Invention as Claimed

6. Independent claim 1: A partially thio-modified aptamer that binds to a TGF- β protein wherein the partially thio-modified aptamer comprises one or more thio-modifications on the aptamer backbone and variations thereof.

Independent claim 78: A partially thio-modified aptamer that binds specifically to TGF- β comprising a sequence and modifications that is at least 80% complementary to SEQ ID NO: 62.

New Rejection

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a **new matter** rejection. Claim 78 requires a sequence and modifications that are at least 80% complementary to SEQ ID NO: 62. While the specification as originally filed disclose SEQ ID NO: 62 and thio-modifications of SEQ ID NO: 62, the specification as originally filed does not teach sequences with 80% complementarity to SEQ ID NO: 62. The original specification is silent with regard to any specific percent complementarity to SEQ ID NO: 62.

Maintained Rejections

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. In addition, the rejections may have been modified to reflect the claim amendments.

Claim Rejections - 35 USC § 112

10. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. Claim 7 reads “wherein the aptamer comprises the sequence and modifications of SEQ ID NO: 62”. In the sequence listing received on October 8, 2004, SEQ ID NO: 62 is identified as the following:

Section 210: 62 (i.e. SEQ ID NO:)

Section 211: 74 (i.e. sequence length)

Section 212: DNA (i.e. sequence type)

Section 213: Artificial Sequence (i.e. organism sequence is from)

Section 220: blank (i.e. features including modifications)

Section 223: Description of Artificial Sequence: Synthetic oligonucleotide (i.e. other information including modifications)

Section 400: cagtccggat gctctagagt gacgtgaaag tgcaatggat ccaggacccc acacgaatct cgtgaagccg agcg (i.e. sequence)

Thus, SEQ ID NO: 62 does not have any modifications. For example, would modifications of SEQ ID NO: 62 include sequences with 10%, 20%, 40%, 80%, etc. complementary/identity; would the addition of a thiol to SEQ ID NO: 62 be a modification; would the removal of the thio-modification required by independent claim 1 be considered the modification in claim 7, would the addition of other chemical compounds, nucleic acids, amino acids, etc. be considered modifications; etc.?

Arguments and Response

11. Applicants' arguments directed to the rejection under 35 USC 112, second paragraph (indefinite), for claim 7 was considered but are not persuasive for the following reasons.

Applicants contend that the claim uses precise language (i.e. not indefinite), applicant does not have to state specifically what the exact amount to be modified or each and every specific modification, and the dependent claim incorporates by reference all the limitations of the independent claim.

Applicants' arguments are not convincing since the phrase "comprises the sequence and modifications of SEQ ID NO: 62" is indefinite. The Office interprets claim language related to SEQ ID NOs: as follows: The phrase "comprises a sequence of SEQ ID NO: ..." requires only a dimer/dinucleotide/dipeptide of the claimed SEQ ID NO: while the phrase "comprises the sequence of SEQ ID NO: ..." (i.e. present claim language) requires the full length sequence of the claimed SEQ ID NO: with open claim language regarding the 5' or 3' end (i.e. any 5' or 3' additions). However, the presently claimed phrase of "comprises the sequence and modifications of SEQ ID NO: 62" is unclear as to the amount of the sequence required by the claim due to the "modifications" language (e.g. full length required, only a portion of the sequence required wherein the modifications are deletions, a sequence with 10% identity wherein the modifications are mutations to 90% of the sequence, etc.). Further exacerbating the issue is that the sequence listing does not discuss any modifications to the sequence and/or "modifications" is much broader in scope than "thio-modifications". Thus, it is unclear if the modifications in claim 7 are referring to the thio-modifications or to other modifications.

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12. Claim 78 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. Claim 78 reads “[a] partially thio-modified aptamer that binds to TGF- β comprising a sequence and modifications that is at least 80% complementary to SEQ ID NO: 62”. For example, would modifications of SEQ ID NO: 62 include mutations that maintain 80% complementarity/identity; would the addition of a thiol to SEQ ID NO: 62 be a modification; would the addition of other chemical compounds, nucleic acids, amino acids, etc. be considered modifications; etc.?

Arguments and Response

13. Applicants’ arguments directed to the rejection under 35 USC 112, second paragraph (indefinite), for claim 7 was considered but are not persuasive for the following reasons.

Applicants contend that the claim uses precise language (i.e. not indefinite), applicant does not have to state specifically what the exact amount to be modified or each and every specific modification, and the dependent claim incorporates by reference all the limitations of the independent claim.

Applicants’ arguments are not convincing since the phrase “comprising a sequence and modifications that is at least 80% complementary to SEQ ID NO: 62” is indefinite. The Office interprets claim language related to SEQ ID NOs: as follows: The phrase “comprises a sequence of SEQ ID NO: ...” requires only a dimer/dinucleotide/dipeptide of the claimed SEQ ID NO: while the phrase “comprises the sequence of SEQ ID NO: ...” requires the full length sequence of the claimed SEQ ID NO: with open claim language regarding the 5’ or 3’ end (i.e. any 5’ or 3’

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additions). While the presently claimed phrase of “comprising a sequence and modifications that is at least 80% complementary to SEQ ID NO: 62” states the amount of complementarity of both the sequence and the modifications to SEQ ID NO: 62, it is unclear if the modifications recited in the claim refer to the thio-modifications or refer to additional modifications. It is noted that claim 78 is independent and does not depend on claim 1 (page 12, last full paragraph of applicants arguments received on February 22, 2008 appears to suggest that claim 78 depends on claim 1).

Withdrawn Rejections

14. The rejection of claims 1-6 and 8-11 under 35 U.S.C. 102(b) as being anticipated by Pagratis et al. U.S. Patent 6,346,611 issued February 12, 2002 is withdrawn in view of the claim amendments received on February 22, 2008.

15. The rejection of claims 1-6 and 8-11 under 35 U.S.C. 102(e) as being anticipated by Pagratis et al. U.S. Patent 6,713,616 filed February 23, 2001 is withdrawn in view of the claim amendments received on February 22, 2008.

16. The rejection of claims 1 and 7 under 35 U.S.C. 102(e) as being anticipated by Rubenfield et al. U.S. Patent 6,551,795 filed February 18, 1999 is withdrawn in view of the claim amendments received on February 22, 2008.

New Rejection

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 1-6 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pagratis et al. U.S. Patent 6,346,611 issued February 12, 2002 and Gorenstein et al. WO 00/24404 published May 4, 2000 (provided by applicants in the IDS).

For present claims 1-6 and 9-11, Pagratis et al. teach aptamers that bind human TGF β 1, TGF β 2, and TGF β 2 dimers wherein the aptamers may comprise a labeling tag, phosphorothioate modifications, backbone modifications, pre- or post-SELEX modifications, and/or be diluted in saline (i.e. pharmaceutically acceptable salts and diluent; please refer to the entire specification particularly the abstract; Figures; columns 1-2, 6-7, 10-13; Examples; Tables; claims 1-5).

However, Pagratis et al. does not teach the amount of backbone modifications or phosphorothioate modifications (i.e. partial, complete, etc.) or the secondary structure of the aptamers (i.e. achiral).

For present claims 1 and 8, Gorenstein et al. teach aptamers with post-selection modification wherein one or more selected nucleotides of aptamers of known sequence are substituted with modified achiral nucleotides particularly achiral thiophosphate nucleotides (please refer to the entire specification particularly the abstract; pages 1, 4-8).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the TGF- β specific aptamers with backbone phosphorothioate modifications taught Pagratis et al. with the partial thio-modifications and achiral structure of aptamers taught by Gorenstein et al.

One having ordinary skill in the art would have been motivated to do this because Gorenstein et al. teach that partial thio-modification of the backbone with achiral nucleotides including achiral thiophosphate nucleotides result in increased nuclease resistance while retaining binding efficiency and selectivity (see the abstract).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the TGF- β specific aptamers with backbone phosphorothioate modifications taught Pagratis et al. with the partial thio-modifications and achiral structure of aptamers taught by Gorenstein et al. because Gorenstein et al. teach that partially thiolated achiral aptamers retain binding specificity (see Examples 1-4 and 6). In addition, Pagratis et al. teach backbone and phosphorothioate modifications of TGF- β specific aptamers and the need to modify the TGF- β aptamers to enhance the half life *in vivo* (see column 7; paragraph spanning columns 12-13; column 13).

Therefore, the modification of the TGF- β specific aptamers with backbone phosphorothioate modifications taught Pagratis et al. with the partial thio-modifications and achiral structure of aptamers taught by Gorenstein et al. render the instant claims *prima facie* obvious.

Allowable Subject Matter

19. The **exact** sequence of SEQ ID NO: 62 was not found in the prior art. An independent claim drawn to a partially thio-modified aptamer comprising **the** nucleic acid of SEQ ID NO: 62 would be free of the prior art.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Patent Examiner, Art Unit 1639

July 31, 2008

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